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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
HORNING, MICHELLE S	
ART UNIT	**PAPER NUMBER**
1648	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,978	SOTO-JARA ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-22,27 and 29-57* is/are pending in the application.

4a) Of the above claim(s) *16,27,33 and 51-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,17-20,30,35,38,40,43-47 and 50* is/are rejected.

7)☒ Claim(s) *21,22,29,31,32,34,36,37,39,41,42,48 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/16/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 5/19/2008. The status of the claims is as follows: claims 15, 17-22, 29-32 and 34-50 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 5/19/2008 is acknowledged. The traversal is on the ground(s) that the claims of Groups I-IV are integrally linked as product and method of use. This is not found persuasive because the product, diagnostic kit, can be practiced with different materials, including by way of antibody binding and other materials as disclosed in the instant specification (pg 3-4). Note that the methods of Groups I and II are drawn to the detection of two distinct proteins. Lastly, the methods do not share the same technical feature and detection of either prion or apoB would not lead to treatment of a prion disease (Group IV). Detection and treatment are classified differently. For these reasons, a search of all of the groups would create much burden.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 17-22, 29-32 and 34-50 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how step (ii) contacting the preparation obtained in step (i) with PrPc or PrPc containing mixtures would lead to step (iii) determining the presence and/or an amount of PrPsc in said sample (see independent claims 15 and 19).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17, 18, 21, 22 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors.

Nature of the invention. The claims are drawn to a method for the diagnosis of any and all prion diseases (see claim 15). Claims 17 and 18 are drawn to the diagnosis of BSE or CJD. Additionally noted is that the method steps include any and all

fragments of ApoB and ApoE proteins. Claims 48-49 are drawn to modulatory compounds which modulate the PrPc-PrPsc transition.

State of the prior art. The instant specification states the following with respect to known prion-related diseases (page 8):

"Prions" are distinct from bacteria, viruses and viroids. Known prions include those which infect animals to cause scrapie, a transmissible, degenerative disease of the nervous system of sheep and goats as well as bovine spongiform encephalopathies (BSE) or mad cow disease and feline spongiform encephalopathies of cats. Four prion diseases known to affect humans are Kuru, Creutzfeldt-Jakob Disease (CJD), Gerstmann-Strassler-Scheinker Disease (GSS), and fatal familial insomnia (FFI) (Prusiner, 1991). As used herein prion includes all forms of prions causing all or any of these diseases or others in any animals used -- and in particular in humans and in domestic farm animals.

The specification also describes the prior art in providing PrPsc detection methods using ApoA ligands (page 3) and PrPsc/ApoH complexes (page 4).

Breadth of the claims. The claims are broad in that they encompass any and all prion-related diseases and any and all ApoB or ApoE fragments. Also note that the specification provides the following definition for fragments (paragraph 41):

The terms "fraction" or "fragment" refer to any fragment of the polypeptidic chain of the compound itself, alone or in combination with related molecules or residues bound to it, for example residues of sugars or phosphates, or aggregates of the original polypeptide or peptide. Such molecules can result also from other modifications which do not normally alter primary sequence, for example in vivo or in vitro of phosphorylation (introduction of phosphotyrosine, phosphoserine, or phosphothreonine residues) or glycosylation (by exposing the peptide to enzymes which affect glycosylation e.g., mammalian glycosylating or deglycosylating enzymes) of a peptide during its synthesis and processing or in further processing steps. Thus, a fragment can encompass a dipeptide.

With respect to claims 48-49, the claims encompass all possible compounds and antibodies which would modulate the PrPc-PrPsc transition.

Working Examples. The examples merely show prion replication via PMCA, lipid raft analysis and LDL binding. There is no working example showing the successful diagnosis of a specific prion-related disease. Further, there are no examples disclosing how to make the modulatory compounds of specific function as claimed in claims 48-49.

Guidance of the specification. The specification fails to provide any guidance in the actual diagnosis of a prion disease, including diagnosis of BSE or CJD (claims 17 and 18). More specifically, the specification does not disclose any guidance in distinguishing among the different prion diseases. The specification does provide guidance in the qualitative (yes or no) detection of PrPsc. Note that the Office defines "diagnosis" as the process of determining the nature of a disease state. The specification fails to disclose a representative number of structurally related “modulatory” compounds (claims 48-49).

Predictability of the art. There is no way one could predict how to successfully apply the claimed methods with the teaching of the instant specification. Further, the artisan would not know the identity of any non-disclosed compounds falling within the scope of claims 48-49 and, as a result, would not know how to make it.

Amount of experimentation necessary. Much experimentation is required in order to achieve the method as claimed (diagnosis). It is not clear how the detection of a PrPsc would lead to the successful diagnosis of the specific prion disease. Experimentation is required with regards to ascertaining the differential structures

across the different prion diseases and the peptides that would selectively bind them. Further, the artisan would be required to identify the structural characteristics of modulatory compounds that would lead to the specific function as claimed in 48-49.

For the reasons discussed above, it would require undue experimentation for on of ordinary skill in the art to use the claimed methods as well as make the underlying required products for the claimed methods.

Claims 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a genus of compounds that specifically modulate the transition of PrPc into PrPsc using the detection assay of claim 20.

The following quotation from section 2163 of the MPEP is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed or through disclosure of a functional characteristic of the claimed genus coupled with a known or disclosed non-functional characteristic (structure) that correlates to the function. Structural identifying characteristics of the genus members are not disclosed. Therefore, the claimed invention is not supported by an adequate written description. Note that not all ApoB antibodies will result in modulating the PrPc-PrPsc transition and specific structural features of the ApoB protein (eg ApoB epitopes) which would lead to this function effect are not disclosed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15, 17-20, 30, 35, 38, 40, 43-45 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Soto et al (2002), Baumann et al (2000) and Huang et al (2001) in further view of Clavey et al (1991, cited).

Soto et al disclose the method of cyclic amplification of protein misfolding (PMCA), including the amplification of infectious TSE protein (see whole document). The authors note that such amplification "offers the possibility of amplifying the amount of PrPsc in a sample, making it detection by existing methods easier" (see page 391). Page 392 provides that PMCA requires a PrPc substrate in high molar excess for conversion. The authors discuss how such a method of amplification combined with sensitive detection methods would allow for the early diagnosis of TSE for both sample and living animals and people (see page 393). This publication does not teach the use of ApoE or its fragments.

Baumann et al provide evidence that ApoE enhances the amyloidogenicity of PrP proteins (see whole document and page 78). Figure 4 demonstrates this enhancement of PrP and beta-amyloid proteins by way of a ThT assay of formed amyloid fibrils. Of note, the authors provide the following statement: "deposits in various amyloidoses and prion diseases include both biochemically and immunohistochemically detectable amounts of apoE. Thus the molecular interaction of apoE seems not to be specific for

AD but more a common characteristic in the development of other amyloidoses as well" (see Discussion, page 82). The author dubbed apoE as a "universal pathological chaperone" and noted that each amyloidogenic fragment tested (prion and beta-amyloid) demonstrated that apoE is mediated through only one common binding site (see page 82).

Huang et al disclose that apoE fragments induce neurofibrillary tangles in neurons (see whole document). More specifically, the authors conclude that carboxyl-terminal-truncated forms of apoE induce such tangles compared to other truncated apoE in neuronal cells.

It would have been obvious to one of ordinary skill in the art to combine the teachings above in order to perform a method of PrPsc detection. One would have been motivated to amplify PrPsc (as taught by Soto et al) and further enhance such the PrPc-PrPsc transition by providing ApoE or its fragments (as taught by Baumann et al or by Huang et al) in order to make its detection easier. Further, the ordinary artisan would have been motivated to screen for drugs which would inhibit the PrPc-PrPsc transition using this method. There would have been a reasonable expectation of success given the methods are well characterized by the prior art, including the successes of the references above. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Lastly, Clavey et al provides that apoE binds LDL receptors. Thus, claims 30, 35, 40 and 50 are rejected given this binding is inherent.

Claims 20, 44, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Soto et al (2002), Baumann et al (2000) and Huang et al (2001) and Naslavsky et al (1997) in further view of Clavey et al (1991, cited).

Claims 20 and 44 are rejected as the teachings apply above. Soto et al, Baumann et al, Huang et al and Clavey et al do not teach using lipid rafts from N2a cells as a source of normal PrPc and substrate (see claims 46 and 47).

Naslavsky et al characterize the detergent-insoluble complexes containing the PrPc and its scrapie isoforms in N2a cells (see whole document). The authors provide that PrPc is localized to rafts and its attachment to rafts is essential for the efficient conversion of PrPc into PrPsc (see Discussion). Lastly, the authors provide an extraction procedure for the isolation and characterization of either the PrPc or the PrPsc raft (whole document). Thus, it would have been obvious to combine the teachings above to perform a screening assay for modulatory compounds using lipid rafts from N2a cells. One would have been motivated to do so given the extraction procedure for the isolation of the PrPc raft is well characterized by Naslavsky et al. There would have been a reasonable expectation of success given the authors provided a successful method. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Matter

The following claims are allowable but are objected to for depending on rejected claims: claims 21, 22, 29, 31, 32, 34, 36, 37, 39, 41, 42, 48 and 49.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/

Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648